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FILE 'HOME' ENTERED AT 10:56:29 ON 30 NOV 2001

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FILE 'MEDLINE' ENTERED AT 10:57:30 ON 30 NOV 2001

FILE 'CAPLUS' ENTERED AT 10:57:30 ON 30 NOV 2001
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=> s 221081-52-3
L1             1 221081-52-3

=> d ibib abs

L1   ANSWER 1 OF 1  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         1999:184237  CAPLUS
DOCUMENT NUMBER:          130:218328
TITLE:                    Oxo-substituted heterocyclic compounds, therapeutic
                          methods, and compositions for inhibiting
                          poly(ADP-ribose) polymerase (PARP) activity
INVENTOR(S):              Li, Jia-He; Tays, Kevin L.; Zhang, Jie
PATENT ASSIGNEE(S):       Guilford Pharmaceuticals Inc., USA
SOURCE:                   PCT Int. Appl., 152 pp.
                          CODEN: PIXXD2
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   11
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.  DATE
     ---------------   ----  --------       ---------------  --------
     WO 9911624         A1   19990311       WO 1998-US18195  19980902
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
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             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
             NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
             UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
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             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     ZA 9808010         A    19990303       ZA 1998-8010     19980902
     ZA 9808011         A    19990303       ZA 1998-8011     19980902
     ZA 9808012         A    19990303       ZA 1998-8012     19980902
     ZA 9808013         A    19990303       ZA 1998-8013     19980902
     ZA 9808015         A    19990303       ZA 1998-8015     19980902
     AU 9892986         A1   19990322       AU 1998-92986    19980902
     EP 1009739         A2   20000621       EP 1998-945833   19980902
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
     BR 9812428         A    20000926       BR 1998-12428    19980902
     NO 2000001002      A    20000427       NO 2000-1002     20000228
     US 6235748         B1   20010522       US 2000-524750   20000314
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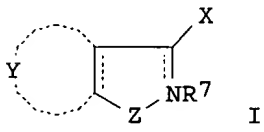
PRIORITY APPLN. INFO.: US 1997-922520 A 19970903
US 1998-79509 A 19980515
US 1998-145180 A 19980901
WO 1998-US18195 W 19980902

OTHER SOURCE(S): MARPAT 130:218328

GI



I

AB PARP-inhibiting oxo-substituted heterocyclic compds., compns. contg. them, therapeutic methods of using them, and processes for making them are disclosed. The compds., contg. at least one ring nitrogen, are I [X = double-bonded O, OH; R7 (when present) = H, lower alkyl; Y = atoms necessary to form fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms; Z = (i) CHR2CHR3 (R2, R3 = H, alkyl, aryl, aralkyl); (ii) R6C=CR3 (R3, R6 = H, lower alkyl, aryl, aralkyl, halo, NO2, COOR7, NR7R8 (R8 = H, C1-C9 alkyl), or R6 and R3 taken together form fused arom. ring, wherein each individual ring has 5-6 ring members); (iii) R2C=N; (i.v.) CR2(OH)NR7; (v) C(O)NR7] or a pharmaceutically acceptable base or acid addn. salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer or mixt. thereof.

REFERENCE COUNT: 22
REFERENCE(S): (1) Anon; 1976, 21, CAPLUS
(3) Banasik, M; JOURNAL OF BIOLOGICAL CHEMISTRY 1992, V267(3), P1569 CAPLUS
(4) Cancer Research Campaign Technology Limited; WO 9524379 A 1995 CAPLUS
(5) Dokunikhin, N; Derivatives of cyclopenta ` k, l, mphenanthridine 1978, 13, P505 CAPLUS
(6) Dokunikhin, N; ZH VSES KHIM O-VA V22(6), P706 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

=>
=> s phenanthridinone
L2 298 PHENANTHRIDINONE

=> s ?phenanthridinone
L3 321 ?PHENANTHRIDINONE

=> s ?phenanthridinone?
L4 349 ?PHENANTHRIDINONE?

=> s parp
L5 2409 PARP

=> s l5 and l4
L6 28 L5 AND L4

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=> duplicate remove l6
DUPLICATE PREFERENCE IS 'MEDLINE, CAPLUS'
KEEP DUPLICATES FROM MORE THAN ONE FILE?  Y/(N):n
PROCESSING COMPLETED FOR L6
L7           18 DUPLICATE REMOVE L6 (10 DUPLICATES REMOVED)

=> d ibib abs 1-18

L7   ANSWER 1 OF 18  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2001:161504  CAPLUS
DOCUMENT NUMBER:          134:202696
TITLE:                    Alkoxy-substituted compounds, methods, and
                          compositions for inhibiting poly(ADP-ribose
polymerase
                          (PARP) activity and treating cardiovascular
                          disease
INVENTOR(S):              Jackson, Paul F.; Maclin, Keith M.; Zhang, Jie
PATENT ASSIGNEE(S):       Guilford Pharmaceuticals Inc., USA
SOURCE:                   U.S., 41 pp., Cont.-in-part of U.S. Ser. No. 79,508.
                          CODEN: USXXAM
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   11
PATENT INFORMATION:

     PATENT NO.        KIND  DATE           APPLICATION NO.   DATE
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     US 6197785         B1   20010306       US 1998-145166    19980901
     ZA 9808010         A    19990303       ZA 1998-8010      19980902
     ZA 9808011         A    19990303       ZA 1998-8011      19980902
     ZA 9808012         A    19990303       ZA 1998-8012      19980902
     ZA 9808013         A    19990303       ZA 1998-8013      19980902
     ZA 9808015         A    19990303       ZA 1998-8015      19980902
     WO 9911628         A1   19990311       WO 1998-US18226   19980902
         W:  AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,
             DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,
             KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
             NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
             UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
         RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
             FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
             CM, GA, GN, GW, ML, MR, NE, SN, TD, TG
     AU 9892991         A1   19990322       AU 1998-92991     19980902
     EP 1012145         A1   20000628       EP 1998-945838    19980902
         R:  AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT,
             IE, FI
PRIORITY APPLN. INFO.:                    US 1997-922520    B2 19970903
                                          US 1998-79508     A2 19980515
                                          US 1998-145166    A  19980901
                                          WO 1998-US18226   W  19980902
OTHER SOURCE(S):          MARPAT 134:202696
GI
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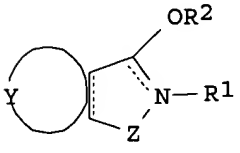

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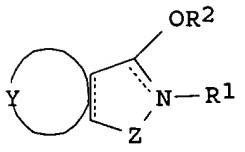

I

AB The invention discloses compds., compns., methods of use, and processes of making I [R1 (when present) = H, lower alkyl; R2 = lower alkyl, aryl, aralkyl, etc.; Y = atoms necessary to form fused 5- to 6-membered ring that is arom. or nonarom. and carbocyclic or heterocyclic; Z = (i) CHR2CHR3 (R2, R3 = H, alkyl, aryl, aralkyl); (ii) R6C:CR3 (R6, R3 = H, lower alkyl, aryl, aralkyl, Cl, Br, NR7R8 (R7, R8 = H, lower alkyl), or R6 and R3, taken together form fused 5- to 6-membered ring that is arom. or nonarom. and carbocyclic or heterocyclic); (iii) R2C:N; (iv) CR2(OH)NR7; (v) C(O)NR7] or a pharmaceutically acceptable salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixts. thereof. The compds. of the invention can be used to treat cardiovascular diseases and to inhibit **PARP** activity.

REFERENCE COUNT: 84

REFERENCE(S):
(1) Albert, A; Journal of the Chemical Society 1956, P1294 CAPLUS
(2) Anon; DE 963184 1957 CAPLUS
(4) Anon; GB 810108 1959 CAPLUS
(7) Anon; BE 628255 1963 CAPLUS
(9) Anon; GB 1474775 1977 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 2 OF 18 MEDLINE DUPLICATE 1

ACCESSION NUMBER: 2001267726 MEDLINE
DOCUMENT NUMBER: 21257723 PubMed ID: 11358842
TITLE: Novel inhibitors of poly(ADP-ribose) polymerase/PARP1 and PARP2 identified using a cell-based screen in yeast.
AUTHOR: Perkins E; Sun D; Nguyen A; Tulac S; Francesco M; Tavana H; Nguyen H; Tugendreich S; Barthmaier P; Couto J; Yeh E; Thode S; Jarnagin K; Jain A; Morgans D; Melese T
CORPORATE SOURCE: Iconix Pharmaceuticals, 320 Logue Avenue, Mountain View, CA 94043, USA.
SOURCE: CANCER RESEARCH, (2001 May 15) 61 (10) 4175-83. Journal code: CNF; 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200106
ENTRY DATE: Entered STN: 20010618
Last Updated on STN: 20010618
Entered Medline: 20010614

AB Multicellular organisms must have means of preserving their genomic integrity or face catastrophic consequences such as uncontrolled cell proliferation or massive cell death. One response is a modification of nuclear proteins by the addition and removal of polymers of ADP-ribose that modulate the properties of DNA-binding proteins involved in DNA repair and metabolism. These ADP-ribose units are added by poly(ADP-ribose) polymerase (**PARP**) and removed by

poly(ADP-ribose) glycohydrolase. Although budding yeast Saccharomyces cerevisiae does not possess proteins with significant sequence similarity to the human **PARP** family of proteins, we identified novel small molecule inhibitors against two family members, PARP1 and PARP2, using a cell-based assay in yeast. The assay was based on the reversal of growth inhibition caused by the heterologous expression of either PARP1 or PARP2.

Validation of the assay was achieved by showing that the growth inhibition was relieved by a mutation in a single residue in the catalytic site of PARP1 or PARP2 or exposure of yeast to a known PARP1 inhibitor, 6(5H)-**phenanthridinone**. In separate experiments, when a putative protein regulator of **PARP** activity, human poly(ADP-ribose) glycohydrolase, was coexpressed with PARP1 or PARP2, yeast growth was restored. Finally, the inhibitors identified by screening the yeast assay are active in a mammalian **PARP** biochemical assay and inhibit PARP1 and PARP2 activity in yeast cell extracts. Thus, our data reflect the strength of using yeast to identify small molecule inhibitors of therapeutically relevant gene families, including those that are not found in yeast, such as **PARP**. The resultant inhibitors have two critical uses (a) as leads for drug development and (b) as tools to dissect cellular function.

L7 ANSWER 3 OF 18 MEDLINE DUPLICATE 2
ACCESSION NUMBER: 2001482406 MEDLINE
DOCUMENT NUMBER: 21417164 PubMed ID: 11526447
TITLE: Poly(ADP-ribose) polymerase inhibitors attenuate necrotic but not apoptotic neuronal death in experimental models of cerebral ischemia.
AUTHOR: Moroni F; Meli E; Peruginelli F; Chiarugi A; Cozzi A; Picca R; Romagnoli P; Pellicciari R; Pellegrini-Giampietro D E
CORPORATE SOURCE: Dipartimento di Farmacologia Preclinica e Clinica, Universita di Firenze, Viale G. Pieraccini 6, I-50139 Florence, Italy.. fmoroni@pharm.unifi.it
SOURCE: CELL DEATH AND DIFFERENTIATION, (2001 Sep) 8 (9) 921-32. Journal code: C7U; 9437445. ISSN: 1350-9047.
PUB. COUNTRY: England: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200111
ENTRY DATE: Entered STN: 20010830
Last Updated on STN: 20011105
Entered Medline: 20011101

AB An excessive activation of poly(ADP-ribose) polymerase (**PARP**) has been proposed to play a key role in post-ischemic neuronal death. We examined the neuroprotective effects of the **PARP** inhibitors benzamide, 6(5H)-**phenanthridinone**, and 3,4-dihydro-5-[4-1(1-piperidinyl)buthoxy]-1(2H)-isoquinolinone in three rodent models of cerebral ischemia. Increasing concentrations of the three **PARP** inhibitors attenuated neuronal injury induced by 60 min oxygen-glucose deprivation (OGD) in mixed cortical cell cultures, but were unable to reduce CA1 pyramidal cell loss in organotypic hippocampal slices exposed to 30 min OGD or in gerbils following 5 min bilateral carotid occlusion. We then examined the necrotic and apoptotic features of OGD-induced neurodegeneration in cortical cells and hippocampal slices using biochemical and morphological approaches. Cortical cells exposed to OGD released lactate dehydrogenase into the medium and displayed

ultrastructural features of necrotic cell death, whereas no caspase-3 activation nor morphological characteristics of apoptosis were observed at any time point after OGD. In contrast, a marked increase in caspase-3 activity was observed in organotypic hippocampal slices after OGD, together with fluorescence and electron microscope evidence of apoptotic neuronal death in the CA1 subregion. Moreover, the caspase inhibitor Z-VAD-FMK reduced OGD-induced CA1 pyramidal cell loss. These findings suggest that **PARP** overactivation may be an important mechanism leading to post-ischemic neurodegeneration of the necrotic but not of the apoptotic type.

L7 ANSWER 4 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 2000:658496 CAPLUS
DOCUMENT NUMBER: 133:232874
TITLE: Di-N-heterocyclic compounds, methods and compositions for inhibiting **PARP** activity, and therapeutic use
INVENTOR(S): Jackson, Paul F.; Maclin, Keith M.; Zhang, Jie
PATENT ASSIGNEE(S): Guilford Pharmaceuticals, Inc., USA
SOURCE: U.S., 44 pp., Cont.-in-part of U.S. Ser. No. 79,510, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6121278	A	20000919	US 1998-145185	19980901
ZA 9808010	A	19990303	ZA 1998-8010	19980902
ZA 9808011	A	19990303	ZA 1998-8011	19980902
ZA 9808012	A	19990303	ZA 1998-8012	19980902
ZA 9808013	A	19990303	ZA 1998-8013	19980902
ZA 9808015	A	19990303	ZA 1998-8015	19980902
WO 9911644	A1	19990311	WO 1998-US18188	19980902
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RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
AU 9892981	A1	19990322	AU 1998-92981	19980902

PRIORITY APPLN. INFO.:			
US 1997-922520	A2	19970903
US 1998-79510	B2	19980515
US 1998-79511	A	19980515
US 1998-145185	A	19980901
WO 1998-US18188	W	19980902

OTHER SOURCE(S): MARPAT 133:232874
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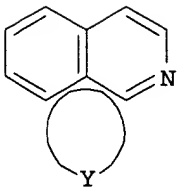


I

AB The invention provides I (Y = atoms necessary to form fused 5- to 6-membered, arom. or non-arom., heterocyclic ring contg. .gtoreq.1 N in 1,3-relationship with N shown; Y may be unsubstituted or substituted with .gtoreq.1 alkyl, alkenyl, cycloalkyl, cycloalkenyl, aralkyl, aryl, etc.), or pharmaceutically acceptable salts, hydrates, esters, solvates, prodrugs, metabolites, stereoisomers, or mixts. thereof, for inhibiting poly(ADP-ribose)polymerase (**PARP**) activity and treating a variety of diseases.

REFERENCE COUNT: 52
REFERENCE(S):
(1) Anon; EP 0355750 1990 CAPLUS
(2) Anon; WO 9524379 1995 CAPLUS
(3) Anon; WO 9529895 1995 CAPLUS
(4) Bach; US 4031097 1977 CAPLUS
(5) Bauer; Int J Oncol 1996, V8, P239 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 5 OF 18 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000510259 MEDLINE
DOCUMENT NUMBER: 20516342 PubMed ID: 11062748
TITLE: Modulation of the antiproliferative activity of anticancer drugs in hematopoietic tumor cell lines by the poly(ADP-ribose) polymerase inhibitor 6(5H)-**phenanthridinone**.
AUTHOR: Holl V; Coelho D; Weltin D; Hyun J W; Dufour P; Bischoff P
CORPORATE SOURCE: Laboratoire de Cancerologie Experimentale et de Radiobiologie (LCER), Universite Louis Pasteur, Faculte de Medecine, Strasbourg, France.
SOURCE: ANTICANCER RESEARCH, (2000 Sep-Oct) 20 (5A) 3233-41. Journal code: 59L. ISSN: 0250-7005.
PUB. COUNTRY: Greece
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200012
ENTRY DATE: Entered STN: 20010322
Last Updated on STN: 20010322
Entered Medline: 20001211

AB Poly (ADP-ribose) polymerase (**PARP**) is involved in the cellular responses to genotoxic damage and its inhibition has been proposed as potentiating anticancer drug activity. Here, we evaluated the ability of the **PARP** inhibitor, 6(5H)-**phenanthridinone**, to modulate the antiproliferative activity of bleomycin, carmustin and doxorubicin in a murine (RDM4) and a human (U937) lymphoma cell lines. 6(5H)-**phenanthridinone** was shown to suppress **PARP** activity with the same potency in both cell lines. At 25 microM, this compound potentiated the activity of carmustin in RDM4 but not in U937 cells. In contrast, 6(5H)-**phenanthridinone** failed to affect the doxorubicin toxicity in murine lymphoma cells, whereas it prevented the cytotoxicity of this drug in the human cell line. Altogether, these findings indicated that 6(5H)-**phenanthridinone** modulates the

cytotoxicity of anticancer agents differently according to the cell type and the drug. Therefore, this **PARP** inhibitor could be considered as the prototype of a new class of adjuncts in cancer chemotherapy.

L7 ANSWER 6 OF 18 MEDLINE DUPLICATE 4
ACCESSION NUMBER: 2000208737 MEDLINE
DOCUMENT NUMBER: 20208737 PubMed ID: 10746948
TITLE: Protection from cytotoxic effects induced by the nitrogen mustard mechlorethamine on human bronchial epithelial cells in vitro.
AUTHOR: Rappeneau S; Baeza-Squiban A; Jeulin C; Marano F
CORPORATE SOURCE: Laboratoire de Cytophysiologie et Toxicologie Cellulaire, Universite Paris VII-Denis Diderot, France.. rappeneau@paris7.jussieu.fr
SOURCE: TOXICOLOGICAL SCIENCES, (2000 Mar) 54 (1) 212-21. Journal code: CZ1; 9805461. ISSN: 1096-6080.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200006
ENTRY DATE: Entered STN: 20000616
Last Updated on STN: 20000616
Entered Medline: 20000602

AB The present study was undertaken to find potent molecules against the toxicity of nitrogen mustard mechlorethamine (HN2) on respiratory epithelial cells, using a human bronchial epithelial cell line (16HBE14o-) as an in vitro model. The compounds examined included inhibitors of poly(ADP-ribose) polymerase (**PARP**), sulfhydryl-group donors as nucleophiles, and iron chelators and inhibitors of lipid peroxidation as antioxidants. Their effectiveness was determined upon observance of metabolic dysfunction induced by HN2 following a 4-h exposure, using (3-(4,5-dimethylthiazole-2-yl)-2,5-diphenyl tetrazolium bromide (MTT) reduction and ATP-level assays as indicators. Moreover, the fluorescent probe, monobromobimane (mBBr), and 2',7'-dichlorofluorescin-diacetate (H2DCF-DA) were used to assess intracellular sulfhydryl and peroxide level modifications by flow cytometry, respectively, following a 3-h exposure. At last, cell death was assessed by flow cytometry using the propidium iodide (PI)-dye-exclusion assay following 24-h exposure. **PARP** inhibitors (niacinamide, 3-aminobenzamide, 6(5H)-**phenanthridinone**), and two sulfhydryl-group donors (N-acetylcysteine, WR-1065) were found to be effective in preventing HN2-induced metabolic dysfunction when added in immediate or delayed treatment with HN2. Only N-acetylcysteine, however, was found to prevent cell death induced by HN2, though it must be present at the time of the HN2 challenge. Flow cytometric measurements of intracellular sulfhydryl levels strongly suggested that N-acetylcysteine and WR-1065 are preventive in alkylation of cellular compounds, mainly by direct extracellular interaction with HN2. **PARP** inhibitors prevent secondary deleterious effects induced by HN2, considering metabolism dysfunction as the endpoint. Elsewhere, the oxidative stress appears to be a side effect in HN2 toxicity only upon considering the inefficiency of several antioxidants.

L7 ANSWER 7 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:184260 CAPLUS

DOCUMENT NUMBER: 130:209323
TITLE: Preparation of **PARP** inhibitors
INVENTOR(S): Jackson, Paul F.; Li, Jia-He; Maclin, Keith M.; Zhang, Jie
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 107 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911649	A2	19990311	WO 1998-US18185	19980902
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ZA 9808010	A	19990303	ZA 1998-8010	19980902
ZA 9808011	A	19990303	ZA 1998-8011	19980902
ZA 9808012	A	19990303	ZA 1998-8012	19980902
ZA 9808013	A	19990303	ZA 1998-8013	19980902
ZA 9808015	A	19990303	ZA 1998-8015	19980902
AU 9893748	A1	19990322	AU 1998-93748	19980902
EP 1012153	A1	20000628	EP 1998-946812	19980902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.:

US 1997-922520	A	19970903
US 1997-922548	A	19970903
US 1998-79512	A	19980515
US 1998-145176	A	19980901
WO 1998-US18185	W	19980902

AB **PARP** inhibitors were prepd. and tested for their activity. E.g., 8-(aminocarbonyl)-4-quinolinecarboxylic acid was prepd.

L7 ANSWER 8 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:184255 CAPLUS
DOCUMENT NUMBER: 130:218330
TITLE: Di-N-heterocyclic compounds, therapeutic methods, and compositions for inhibiting poly(ADP-ribose) polymerase (**PARP**) activity
INVENTOR(S): Jackson, Paul F.; Maclin, Keith M.; Zhang, Jie
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 130 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

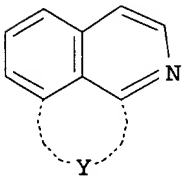
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911644	A1	19990311	WO 1998-US18188	19980902
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE,				

DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG,
KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX,
NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT,
UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,
FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI,
CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

US 6121278	A	20000919	US 1998-145185		19980901
ZA 9808010	A	19990303	ZA 1998-8010		19980902
ZA 9808011	A	19990303	ZA 1998-8011		19980902
ZA 9808012	A	19990303	ZA 1998-8012		19980902
ZA 9808013	A	19990303	ZA 1998-8013		19980902
ZA 9808015	A	19990303	ZA 1998-8015		19980902
AU 9892981	A1	19990322	AU 1998-92981		19980902

PRIORITY APPLN. INFO.:	US 1997-922520	A	19970903
	US 1998-79511	A	19980515
	US 1998-145185	A	19980901
	US 1998-79510	B2	19980515
	WO 1998-US18188	W	19980902

OTHER SOURCE(S): MARPAT 130:218330
GI



I

AB Compds. I [Y = atoms necessary to form fused 5- to 6-membered, arom. or non-arom., (un)substituted heterocyclic ring contg. .gtoreq.1 N in a 1,3-relationship with N depicted] or a pharmaceutically acceptable salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixt. thereof, are disclosed for inhibiting **PARP** activity.

REFERENCE COUNT: 5
REFERENCE(S):
(1) Banasik, M; JOURNAL OF BIOLOGICAL CHEMISTRY 1992, V267(3), P1569 CAPLUS
(2) Cancer Research Campaign Technology Limited; WO 9524379 A 1995 CAPLUS
(3) Griffin, R; ANTI-CANCER DRUG DESIGN 1995, V10(6), P507 CAPLUS
(4) Suto, M; ANTI-CANCER DRUG DESIGN 1991, V6(2), P107 CAPLUS
(5) West, M; US 5589483 A 1996 CAPLUS

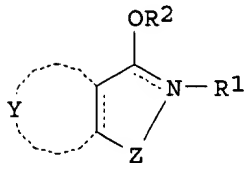
L7 ANSWER 9 OF 18 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1999:184241 CAPLUS
DOCUMENT NUMBER: 130:218329
TITLE: Alkoxy-substituted heterocyclic compounds, therapeutic methods, and compositions for inhibiting poly(ADP-ribose) polymerase (**PARP**) activity
INVENTOR(S): Jackson, Paul F.; Maclin, Keith M.; Zhang, Jie
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 151 pp.

CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911628	A1	19990311	WO 1998-US18226	19980902
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 6197785	B1	20010306	US 1998-145166	19980901
ZA 9808010	A	19990303	ZA 1998-8010	19980902
ZA 9808011	A	19990303	ZA 1998-8011	19980902
ZA 9808012	A	19990303	ZA 1998-8012	19980902
ZA 9808013	A	19990303	ZA 1998-8013	19980902
ZA 9808015	A	19990303	ZA 1998-8015	19980902
AU 9892991	A1	19990322	AU 1998-92991	19980902
EP 1012145	A1	20000628	EP 1998-945838	19980902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				

PRIORITY APPLN. INFO.: US 1997-922520 A 19970903
US 1998-79508 A 19980515
US 1998-145166 A 19980901
WO 1998-US18226 W 19980902

OTHER SOURCE(S): MARPAT 130:218329
GI



I

AB The invention discloses **PARP**-inhibiting alkoxy-substituted heterocyclic compds., compns., therapeutic methods of use, and processes of making these compds. The compds. are I [R1 (when present) = H, lower alkyl; R2 = lower alkyl, aryl, aralkyl, lower alkanoyl, (CH2)n(CHOH)y(CH2)mA (n = 1-4; yr = 0, 1; m = 0-5; A = cycloalkyl, cycloalkenyl, lower alkanoyl, aryl, aralkyl, NH2, etc.); Y = atoms necessary to form fused 5- to 6-membered ring that is arom. or nonarom. and carbocyclic or heterocyclic; Z = (i) CHR2CHR3 (R2, R3 = H, alkyl, aryl, aralkyl); (ii) R6C=CR3 (R6, R3 = H, lower alkyl, aryl, etc., or R6 and R3 taken together form fused 5- to 6-membered ring that is arom. or nonarom. and carbocyclic or heterocyclic); (iii) R2C=N; (i.v.) CR2(OH)NR7; (v) C(O)NR7; R7 = H, lower alkyl] or a pharmaceutically acceptable salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixts. thereof.

REFERENCE COUNT: 25

REFERENCE(S):

(1) Albert, A; JOURNAL OF THE CHEMICAL SOCIETY 1956, P1294 CAPLUS
(2) Asta Medica Ag; EP 0539805 A 1993 CAPLUS
(3) Banasik, M; JOURNAL OF BIOLOGICAL CHEMISTRY 1992, V267(3), P1569 CAPLUS
(4) Cancer Research Campaign Technology Limited; WO 9524379 A 1995 CAPLUS
(5) Cassella Farbwerke Mainkur Ag; DE 963184 C 1957 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

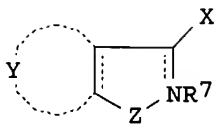
L7 ANSWER 10 OF 18 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:184237 CAPLUS
DOCUMENT NUMBER: 130:218328
TITLE: Oxo-substituted heterocyclic compounds, therapeutic methods, and compositions for inhibiting poly(ADP-ribose) polymerase (**PARP**) activity
INVENTOR(S): Li, Jia-He; Tays, Kevin L.; Zhang, Jie
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 152 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911624	A1	19990311	WO 1998-US18195	19980902
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ZA 9808010	A	19990303	ZA 1998-8010	19980902
ZA 9808011	A	19990303	ZA 1998-8011	19980902
ZA 9808012	A	19990303	ZA 1998-8012	19980902
ZA 9808013	A	19990303	ZA 1998-8013	19980902
ZA 9808015	A	19990303	ZA 1998-8015	19980902
AU 9892986	A1	19990322	AU 1998-92986	19980902
EP 1009739	A2	20000621	EP 1998-945833	19980902
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
BR 9812428	A	20000926	BR 1998-12428	19980902
NO 2000001002	A	20000427	NO 2000-1002	20000228
US 6235748	B1	20010522	US 2000-524750	20000314

PRIORITY APPLN. INFO.:			
US 1997-922520	A	19970903	
US 1998-79509	A	19980515	
US 1998-145180	A	19980901	
WO 1998-US18195	W	19980902	

OTHER SOURCE(S): MARPAT 130:218328
GI



I

AB **PARP**-inhibiting oxo-substituted heterocyclic compds., compns. contg. them, therapeutic methods of using them, and processes for making them are disclosed. The compds., contg. at least one ring nitrogen, are I

[X = double-bonded O, OH; R7 (when present) = H, lower alkyl; Y = atoms necessary to form fused mono-, bi- or tricyclic, carbocyclic or heterocyclic ring, wherein each individual ring has 5-6 ring member atoms;

Z = (i) CHR2CHR3 (R2, R3 = H, alkyl, aryl, aralkyl); (ii) R6C=CR3 (R3, R6 = H, lower alkyl, aryl, aralkyl, halo, NO2, COOR7, NR7R8 (R8 = H, C1-C9 alkyl), or R6 and R3 taken together form fused arom. ring, wherein each individual ring has 5-6 ring members); (iii) R2C=N; (i.v.) CR2(OH)NR7; (v)

C(O)NR7] or a pharmaceutically acceptable base or acid addn. salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer or mixt. thereof.

REFERENCE COUNT: 22

REFERENCE(S):

(1) Anon; 1976, 21, CAPLUS

(3) Banasik, M; JOURNAL OF BIOLOGICAL CHEMISTRY 1992, V267(3), P1569 CAPLUS

(4) Cancer Research Campaign Technology Limited; WO 9524379 A 1995 CAPLUS

(5) Dokunikhin, N; Derivatives of cyclopenta ` k, l, mphenanthridine 1978, 13, P505 CAPLUS

(6) Dokunikhin, N; ZH VSES KHIM O-VA V22(6), P706 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 11 OF 18 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1999:184236 CAPLUS

DOCUMENT NUMBER: 130:218327

TITLE: Thioalkyl-substituted heterocyclic compounds, therapeutic methods, and compositions for inhibiting poly(ADP-ribose) polymerase (**PARP**) activity

INVENTOR(S): Jackson, Paul F.; Maclin, Keith M.; Zhang, Jie

PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA

SOURCE: PCT Int. Appl., 130 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent

LANGUAGE: English

FAMILY ACC. NUM. COUNT: 11

PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911623	A1	19990311	WO 1998-US18184	19980902

W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM

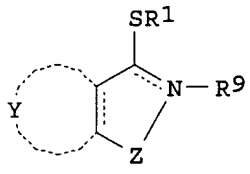
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES,

FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

ZA 9808010	A	19990303	ZA 1998-8010		19980902
ZA 9808011	A	19990303	ZA 1998-8011		19980902
ZA 9808012	A	19990303	ZA 1998-8012		19980902
ZA 9808013	A	19990303	ZA 1998-8013		19980902
ZA 9808015	A	19990303	ZA 1998-8015		19980902
AU 9892978	A1	19990322	AU 1998-92978		19980902
PRIORITY APPLN. INFO.:			US 1997-922520	A	19970903
			US 1998-79513	A	19980515
			US 1998-145179	A	19980901
			WO 1998-US18184	W	19980902

OTHER SOURCE(S): MARPAT 130:218327

GI



I

AB Compds. I [R1 = lower alkyl, lower alkenyl, lower alkynyl; R9 (when present) = H, lower alkyl; Y = atoms necessary to form fused 5- to 6-membered ring that is arom. or nonarom. and carbocyclic or heterocyclic;
Z = (i) CHR2CHR3 (R2, R3 = H, alkyl, aryl, aralkyl); (ii) R6C=CR3 (R6, R3 = H, lower alkyl, aryl, aralkyl, Cl, Br, NR7R8 (R7, R8 = H, lower alkyl) or R6 and R3 taken together form fused 5- to 6-membered ring that is arom.
or nonarom. and carbocyclic or heterocyclic); (iii) R2C=N; (i.v.) CR2(OH)NR7; (v) C(O)NR7], or a pharmaceutically acceptable salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixts. thereof, are disclosed, as are therapeutic methods and compns. for inhibiting poly(ADP-ribose) polymerase (**PARP**) activity.

REFERENCE COUNT: 20
REFERENCE(S):
(1) Albert, A; JOURNAL OF THE CHEMICAL SOCIETY 1959, P2384 CAPLUS
(2) Aspro Nicholas Ltd; GB 1379111 A 1975 CAPLUS
(3) Asta Medica Ag; EP 0539805 A 1993 CAPLUS
(4) Banasik, M; JOURNAL OF BIOLOGICAL CHEMISTRY 1992, V267(3), P1569 CAPLUS
(6) Cancer Research Campaign Technology Limited; WO 9524379 A 1995 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 12 OF 18 CAPLUS COPYRIGHT 2001 ACS

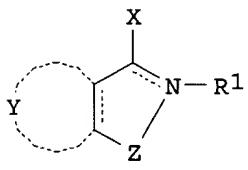
ACCESSION NUMBER: 1999:184235 CAPLUS
DOCUMENT NUMBER: 130:218326
TITLE: Amino-substituted heterocyclic compounds, therapeutic methods, and compositions for inhibiting poly(ADP-ribose) polymerase (**PARP**) activity
INVENTOR(S): Jackson, Paul F.; Maclin, Keith M.; Zhang, Jie
PATENT ASSIGNEE(S): Guilford Pharmaceuticals Inc., USA
SOURCE: PCT Int. Appl., 137 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 11
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9911622	A1	19990311	WO 1998-US18187	19980902
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
ZA 9808010	A	19990303	ZA 1998-8010	19980902
ZA 9808011	A	19990303	ZA 1998-8011	19980902
ZA 9808012	A	19990303	ZA 1998-8012	19980902
ZA 9808013	A	19990303	ZA 1998-8013	19980902
ZA 9808015	A	19990303	ZA 1998-8015	19980902
AU 9892980	A1	19990322	AU 1998-92980	19980902

PRIORITY APPLN. INFO.:
US 1997-922520 A 19970903
US 1998-79507 A 19980515
US 1998-145177 A 19980901
WO 1998-US18187 W 19980902

OTHER SOURCE(S): MARPAT 130:218326
GI



I

AB Compds. I [R1 (when present) = H, lower alkyl; X = NR4R5 (R4, R5 = H, lower alkyl, aralkyl, aryl, etc.); Y = atoms necessary to form fused 5- to 6-membered ring that is arom. or nonarom. and carbocyclic or heterocyclic; Z = (i) CHR2CHR3 (R2, R3 = H, alkyl, aryl, aralkyl); (ii) R6C=CR3 (R6, R3 = H, lower alkyl, aryl, aralkyl, chlorine, bromine, NR7R8 (R7, R8 = H, lower alkyl), or R6 and R3 taken together form fused 5- to 6-membered ring that is arom. or nonarom. and carbocyclic or heterocyclic); (iii) R2C=N; (i.v.) CR2(OH)NR7; (v) C(O)NR7], or a pharmaceutically acceptable salt, hydrate, ester, solvate, prodrug, metabolite, stereoisomer, or mixt. thereof, pharmaceutical compns. contg. them, therapeutic methods for using them , and processes for making them are disclosed.

REFERENCE COUNT: 24
REFERENCE(S):
(1) Aspro Nicholas Ltd; GB 1545767 A 1979 CAPLUS
(2) Astra Pharmaceuticals Ltd; WO 9738977 A 1997 CAPLUS
(3) Banasik, M; JOURNAL OF BIOLOGICAL CHEMISTRY 1992, V267(3), P1569 CAPLUS
(5) Cancer Research Campaign Technology Limited; WO

9524379 A 1995 CAPLUS
(6) Diana, G; JOURNAL OF MEDICINAL CHEMISTRY 1977, V20(3), P449 CAPLUS
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L7 ANSWER 13 OF 18 MEDLINE DUPLICATE 5
ACCESSION NUMBER: 1999430589 MEDLINE
DOCUMENT NUMBER: 99430589 PubMed ID: 10500802
TITLE: Effects of **PARP** inhibition on drug and Fas-induced apoptosis in leukaemic cells.
AUTHOR: Richardson D S; Allen P D; Kelsey S M; Newland A C
CORPORATE SOURCE: Department of Haematology, St. Bartholomew's and Royal London School of Medicine, United Kingdom..
d.s.richardson@mds.qmw.ac.uk
SOURCE: ADVANCES IN EXPERIMENTAL MEDICINE AND BIOLOGY, (1999) 457 267-79.
Journal code: 2LU; 0121103. ISSN: 0065-2598.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199911
ENTRY DATE: Entered STN: 20000111
Last Updated on STN: 20000111
Entered Medline: 19991104

AB Poly (ADP-ribose) polymerase (**PARP**) is activated following binding to DNA strand breaks and is cleaved in cells undergoing apoptosis.

Work predominantly in murine systems has suggested that inhibitors of **PARP** might potentiate the effects of chemotherapeutic agents and be used as adjuncts to cancer therapy. Therefore, we studied the role of **PARP** in drug-induced apoptosis in HL-60, myeloid leukaemia cells and found that pre-treatment with 3-aminobenzamide (3AB) or 6(5H)-**phenanthridinone**, inhibitors of **PARP**, resulted in resistance to, rather than potentiation of apoptotic death induced by DNA-damaging agents, idarubicin, etoposide and fludarabine, as determined by flow cytometry, following propidium iodide staining. 3AB treated CEM/VLB100, mdr-expressing human lymphoblastic leukaemia cells were also found to be more resistant to idarubicin compared to cells treated with idarubicin alone, however, apoptosis was not reduced in parental CCRF-CEM cells under the same conditions. Similar results were obtained using agents with primary modes of action which do not involve DNA damage, vinblastine and a fas-ligating antibody (CH11). The precise role of **PARP** has yet to be defined but might involve effects on cell cycle progression. We conclude that **PARP** activation appears to be involved in apoptosis in certain leukaemic cell lines and that these effects are independent of lineage or p-glycoprotein. Constitutive failure to activate **PARP** might be responsible for conferring resistance to apoptosis.

L7 ANSWER 14 OF 18 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1998114288 MEDLINE
DOCUMENT NUMBER: 98114288 PubMed ID: 9453543
TITLE: Peroxynitrite and hydrogen peroxide induced cell death in the NSC34 neuroblastoma x spinal cord cell line: role of poly (ADP-ribose) polymerase.
AUTHOR: Cookson M R; Ince P G; Shaw P J
CORPORATE SOURCE: Newcastle General Hospital, and Department of Neurology, University of Newcastle, Newcastle upon Tyne, England, UK.

SOURCE: JOURNAL OF NEUROCHEMISTRY, (1998 Feb) 70 (2) 501-8.
Journal code: JAV; 2985190R. ISSN: 0022-3042.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199802
ENTRY DATE: Entered STN: 19980306
Last Updated on STN: 19980306
Entered Medline: 19980224

AB The reaction of superoxide and nitric oxide results in the formation of peroxynitrite, a long lived and highly reactive oxidant species. It has been suggested that the formation of peroxynitrite in vivo may contribute to cell death in some neurological conditions. We have examined the effect of peroxynitrite on cell death in the NSC34 spinal cord cell line. A brief (30 min) exposure to either peroxynitrite or hydrogen peroxide caused delayed cell death with an EC50 for both of approximately 1 mM. Cell death was prevented by the RNA synthesis inhibitor actinomycin D and included DNA damage as an early event. We sought to clarify the potential role of the DNA binding enzyme poly(ADP-ribose) polymerase (**PARP**) in cell death in these cells. Several **PARP** inhibitors [benzamide, 3-aminobenzamide, nicotinamide, and 6(5H)-**phenanthridinone**] prevented cell death, but the inactive analogue benzoic acid did not. However, there was no evidence of cleavage of **PARP**, which occurs in apoptosis via the activation of the caspase CPP32. Therefore, we suggest that **PARP** contributes to neuronal injury as an early event, probably by lethal NAD depletion, without any requirement for proteolytic cleavage.

L7 ANSWER 15 OF 18 MEDLINE DUPLICATE 7
ACCESSION NUMBER: 1998077273 MEDLINE
DOCUMENT NUMBER: 98077273 PubMed ID: 9416791
TITLE: Effect of 6(5H)-**phenanthridinone**, a poly (ADP-ribose)polymerase inhibitor, and ionizing radiation on the growth of cultured lymphoma cells.
AUTHOR: Weltin D; Holl V; Hyun J W; Dufour P; Marchal J; Bischoff P
CORPORATE SOURCE: Laboratoire de Cancerologie Experimentale et de Radiobiologie, Institut d'Hematologie et d'Immunologie, Faculte de Medecine, Strasbourg, France.
SOURCE: INTERNATIONAL JOURNAL OF RADIATION BIOLOGY, (1997 Dec) 72 (6) 685-92.
Journal code: IRB; 8809243. ISSN: 0955-3002.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199801
ENTRY DATE: Entered STN: 19980129
Last Updated on STN: 19980129
Entered Medline: 19980115

AB The ability of 6(5H)-**phenanthridinone** (Phen), a new potent poly(ADP-ribose)polymerase (**PARP**) inhibitor, to potentiate the effect of ionizing radiation on tumour cells was evaluated. RDM4 murine lymphoma cells were irradiated using a 60Co panoramic source and then examined for their growth, cell cycle distribution and apoptosis. Phen

(100 microM) was found to inhibit more than 90% of the **PARP** activity in control and irradiated cells. Cell proliferation was assessed using Alamar Blue, a new fluorometric assay. Phen was found to sharply increase the radiation-induced inhibition of cell proliferation. Indeed, at 2.5 Gy the relative cell number of Phen-treated cells was 60% below control levels. At the same radiation dose, the G2M arrest was also significantly reinforced by the addition of Phen. Furthermore, this **PARP** inhibitor was shown to significantly increase the amount of DNA fragmentation as revealed by the DNA migration pattern in agarose gel electrophoresis. Comparable results were obtained with 3-aminobenzamide, another **PARP** inhibitor, but at concentrations 200-fold higher. Taken together, these results indicate the potential interest of Phen as a valuable pharmacological probe for investigating the role of **PARP** in cellular responses to radiation. They also suggest a possible use of Phen as an adjuvant in radiotherapy.

L7 ANSWER 16 OF 18 MEDLINE DUPLICATE 8
ACCESSION NUMBER: 96221541 MEDLINE
DOCUMENT NUMBER: 96221541 PubMed ID: 8645333
TITLE: N-acetylcysteine protects lymphocytes from nitrogen mustard-induced apoptosis.
AUTHOR: Weltin D; Aupeix K; Iltis C; Cuillerot J M; Dufour P; Marchal J; Bischoff P
CORPORATE SOURCE: Institut d'Hematologie et d'Immunologie, Strasbourg, France.
SOURCE: BIOCHEMICAL PHARMACOLOGY, (1996 May 3) 51 (9) 1123-9. Journal code: 9Z4; 0101032. ISSN: 0006-2952.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199607
ENTRY DATE: Entered STN: 19960726
Last Updated on STN: 19960726
Entered Medline: 19960715

AB The ability of the antioxidant N-acetylcysteine to prevent apoptosis induced in lymphocytes by nitrogen mustard (HN2) was investigated. HN2 caused a concentration-dependent induction of apoptosis on C3H murine spleen cells, as identified by two criteria: morphological features revealed by microscopical observations and DNA fragmentation visualized by the characteristic "ladder" pattern observed upon agarose gel electrophoresis, as well as by hypodiploid DNA-containing cells revealed by the flow cytometric analysis of propidium iodide labelled cells. The antioxidant N-acetylcysteine (NAC) was found to markedly reduce the occurrence of HN2-induced apoptosis in these cells. This protective effect will still obtained when NAC was added 30 min after HN2. In contrast, the pretreatment of spleen cells with this antioxidant did not provide any significant protection. We also showed that lymphocytes protected by NAC are still able to respond to a mitogenic stimulation. To gain some insight into the mechanisms underlying the cytoprotective action of NAC against HN2, we tested whether or not poly(ADP-ribose) polymerase (**PARP**, EC 2.4.2.30), a nuclear enzyme that participates in the triggering of apoptosis induced by alkylating agents, is involved. We report that 6(5H)-**phenanthridinone**, a potent **PARP** inhibitor, did not affect the ability of NAC to prevent HN2-induced apoptosis under our

experimental conditions. Thus, the exact mechanism by which NAC protects lymphocytes from HN2 cytotoxicity has yet to be determined.

L7 ANSWER 17 OF 18 MEDLINE DUPLICATE 9
ACCESSION NUMBER: 95403040 MEDLINE
DOCUMENT NUMBER: 95403040 PubMed ID: 7672878
TITLE: Immunosuppressive activities of 6(5H)-**phenanthridinone**, a new poly(ADP-ribose)polymerase inhibitor.
AUTHOR: Weltin D; Picard V; Aupeix K; Varin M; Oth D; Marchal J; Dufour P; Bischoff P
CORPORATE SOURCE: Institut d'Hematologie et d'Immunologie, Strasbourg, France.
SOURCE: INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, (1995 Apr) 17 (4) 265-71.
Journal code: GRI; 7904799. ISSN: 0192-0561.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199510
ENTRY DATE: Entered STN: 19951026
Last Updated on STN: 19951026
Entered Medline: 19951018
AB 6(5H)-**phenanthridinone**, a recently identified poly(ADP-ribose)polymerase (**PARP**) inhibitor, is able, at micromolar concentrations, to inhibit concanavalin A-induced lymphocyte proliferation and to potentiate the effect of gamma radiation upon murine spleen cells. When added at the onset of a mixed lymphocyte culture, this compound strongly depresses the induction of primary allogeneic (anti-H2k) cytotoxic T-lymphocytes (CTLs). Lymphokine-activated killer (LAK) induction was also found to be impaired by the **PARP** inhibitor. Taken together, these results clearly indicate that **PARP** plays a key-role in immune reactions involving cytotoxicity and that 6(5H)-**phenanthridinone** could be considered as a potent immunomodulator.

L7 ANSWER 18 OF 18 MEDLINE DUPLICATE 10
ACCESSION NUMBER: 95218234 MEDLINE
DOCUMENT NUMBER: 95218234 PubMed ID: 7703525
TITLE: Effect of 6(5H)-**phenanthridinone**, an inhibitor of poly(ADP-ribose) polymerase, on cultured tumor cells.
AUTHOR: Weltin D; Marchal J; Dufour P; Potworowski E; Oth D; Bischoff P
CORPORATE SOURCE: Institut d'Hematologie et d'Immunologie, Strasbourg, France.
SOURCE: ONCOLOGY RESEARCH, (1994) 6 (9) 399-403.
Journal code: BBN; 9208097. ISSN: 0965-0407.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199505
ENTRY DATE: Entered STN: 19950518
Last Updated on STN: 19970203
Entered Medline: 19950511
AB By catalyzing posttranslational modifications of nuclear proteins, poly(ADP-ribose) polymerase (**PARP**) controls their functions and therefore constitutes an enzyme of crucial importance in tumor development. In this study, we have investigated the action of 6(5H)-

phenanthridinone, an isoquinoline derivative and one of the most potent **PARP** inhibitors described so far, on RDM4 murine lymphoma cells in culture. We also examined whether this compound could act synergistically with an antineoplastic drug in tumor-cell destruction. Our results demonstrate that a marked inhibition of **PARP** activity can be obtained in whole cells after a short incubation, and that this compound, when associated with an alkylating agent, dichloro-2,2' N-methyldiethylamine (chloromethine), leads to a marked drop in the RDM4 proliferation, indicative of a synergy between the two compounds.

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=> s ischemia
L8      139651 ISCHEMIA

=> d hist

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     FILE 'MEDLINE, CAPLUS' ENTERED AT 10:57:30 ON 30 NOV 2001
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L2          298 S PHENANTHRIDINONE
L3          321 S ?PHENANTHRIDINONE
L4          349 S ?PHENANTHRIDINONE?
L5         2409 S PARP
L6           28 S L5 AND L4
L7           18 DUPLICATE REMOVE L6 (10 DUPLICATES REMOVED)
L8       139651 S ISCHEMIA

=> s l8 and l4
L9           15 L8 AND L4

=> s l9 not l6
L10           6 L9 NOT L6

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L11  ANSWER 1 OF 6  CAPLUS  COPYRIGHT 2001 ACS
ACCESSION NUMBER:         2001:478104  CAPLUS
DOCUMENT NUMBER:          135:257126
TITLE:                    Synthesis of substituted 5[H]phenanthridin-6-ones as
                          potent poly(ADP-ribose)polymerase-1 (PARP1)
inhibitors
AUTHOR(S):                Li, J.-H.; Serdyuk, L.; Ferraris, D. V.; Xiao, G.;
                          Tays, K. L.; Kletzly, P. W.; Li, W.; Lautar, S.;
                          Zhang, J.; Kalish, V. J.
CORPORATE SOURCE:         Guilford Pharmaceuticals Inc., Baltimore, MD, 21224,
                          USA
SOURCE:                   Bioorg. Med. Chem. Lett. (2001), 11(13), 1687-1690
                          CODEN: BMCLE8; ISSN: 0960-894X
PUBLISHER:                Elsevier Science Ltd.
DOCUMENT TYPE:            Journal
LANGUAGE:                 English
AB   Substituted 6(5H)-phenanthridinones were synthesized and found
     to be potent PARP1 inhibitors.  Among the 28 compds. prepd., some showed
     not only low IC50 values (3,8-dichloro-6(5H)-phenanthridinone,
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10 nM) but also desirable water soly. characteristics. These compds. were screened as inhibitors of poly(ADP-ribose)polymerase-1 [i.e., PARP1; also known as poly(ADP-ribose) synthetase or poly(adenosine diphosphoribose) synthetase]. These properties, which are superior to the common PARP1 inhibitors such as benzamides and 1-isoquinolinones, are essential for potential therapeutic usage. The variety of compds. allows SAR anal. of favored substituents and substituted positions on 5(H)phenanthridin-6-one ring.

REFERENCE COUNT: 13

REFERENCE(S):
(2) Banasik, M; J Biol Chem 1992, V267, P1569 CAPLUS
(3) Cerbai, G; Farmaco, Ed Sci 1972, V27, P939 CAPLUS
(4) Chida, N; Tetrahedron Lett 1991, V32, P4525 CAPLUS
(5) Ha, H; Neurobiology of Disease 2000, V7, P225 CAPLUS
(7) Ling, C; J Chem Soc 1964, P1825 CAPLUS

ALL CITATIONS AVAILABLE IN THE RE FORMAT

L11 ANSWER 2 OF 6 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 2000:756679 CAPLUS
DOCUMENT NUMBER: 133:305615
TITLE: **Phenanthridinones** as neurotrophin potentiators
INVENTOR(S): Isono, Fujio; Fujii, Miyuki; Aoyagi, Atsushi
PATENT ASSIGNEE(S): Sankyo Co., Ltd., Japan
SOURCE: PCT Int. Appl., 38 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000063179	A1	20001026	WO 2000-JP2534	20000419
W: AU, BR, CA, CN, CZ, HU, ID, IL, IN, KR, MX, NO, NZ, PL, RU, TR, US, ZA				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 2001002572	A2	20010109	JP 2000-116590	20000418

PRIORITY APPLN. INFO.: JP 1999-110766 A 19990419

AB This document discloses neurotrophin potentiators which contain 6(5H)-**phenanthridinone** derivs. (Markush structure given) and are useful as preventive or therapeutic drugs for nerve degeneration diseases. The pharmacol. activities of 1-amino-3,8-dichloro-6(5H)-**phenanthridinone** are given. Formulations are given.

REFERENCE COUNT: 5

REFERENCE(S):
(1) Guilford Pharmaceuticals Inc; EP 1009739 A2 CAPLUS
(2) Guilford Pharmaceuticals Inc; WO 9911624 A1 1999 CAPLUS
(3) Takeda Chemical Industries Ltd; JP 115779 A
(4) Takeda Chemical Industries Ltd; US 6030967 A CAPLUS
(5) Takeda Chemical Industries Ltd; WO 9807705 A1 1998 CAPLUS

L11 ANSWER 3 OF 6 CAPLUS COPYRIGHT 2001 ACS

ACCESSION NUMBER: 1998:366893 CAPLUS
DOCUMENT NUMBER: 129:54301
TITLE: Preparation of tricyclic benzazepine vasopressin antagonists
INVENTOR(S): Albright, Jay Donald; Reich, Marvin Fred
PATENT ASSIGNEE(S): American Cyanamid Co., USA
SOURCE: U.S., 103 pp. Cont.-in-part of U. S. 5,512,563.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5760031	A	19980602	US 1996-637911	19960425
US 5512563	A	19960430	US 1994-254823	19940613

PRIORITY APPLN. INFO.: US 1993-100003 B2 19930729
US 1994-254823 A2 19940613
OTHER SOURCE(S): MARPAT 129:54301
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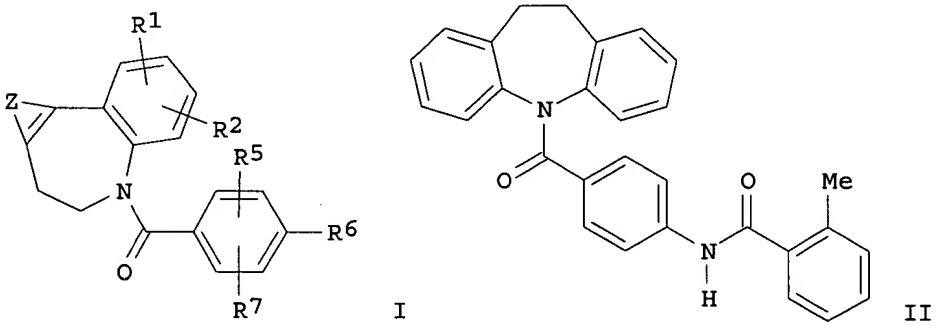


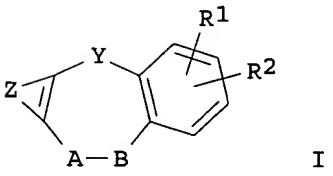
AB The title compds. [I; R1 = H, Cl, F, etc.; R2 = H, Cl, Br, etc.; R1R2 = methylenedioxy, ethylenedioxy; R5 = H, Me, Et, etc.; R6 = N(Ra)COAr', CON(Ra)Ar', etc. (Ra = H, Me, Et; Ar' = (un)substituted Ph, thienyl, etc.); R7 = H, Me, Et, etc.; Z = (un)substituted fused oxazole, Ph], which exhibit antagonist activity at V1 and/or V2 receptors and in vivo vasopressin antagonist activity as well as antagonist activity at oxytocin receptors, and as such useful in treating diseases characterized by excess renal reabsorption of water (e.g., congestive heart failure, nephrotic syndrome, hyponatremia, coronary vasospasm, cardiac **ischemia**, renal vasospasm, liver cirrhosis, brain edema, cerebral **ischemia**, cerebral hemorrhage-stroke), were prepd. Thus, reaction of 4-[(2-methylbenzoyl)amino]benzoyl chloride with 10,11-dihydro-5H-dibenz[b,f]azepine in the presence of 4-(dimethylamino)pyridine in pyridine at 80.degree. for 18 h followed by the addn. of NaH afforded the compd. II which showed IC50 of 2.5 .mu.M against rat hepatic V1 receptor binding and IC50 of 0.86 .mu.M against rat kidney medullary V2 receptor binding.

L11 ANSWER 4 OF 6 CAPLUS

ACCESSION NUMBER: 1998:289524 CAPLUS
DOCUMENT NUMBER: 128:321569
TITLE: Preparation of tricyclic benzazepine vasopressin antagonists
INVENTOR(S): Albright, Jay Donald; Reich, Marvin Fred
PATENT ASSIGNEE(S): American Cyanamid Co., USA
SOURCE: U.S., 101 pp. Cont.-in-part of U.S. Ser. No. 5,512,563.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 10
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 5747487	A	19980505	US 1996-638067	19960425
US 5512563	A	19960430	US 1994-254823	19940613

PRIORITY APPLN. INFO.: US 1993-100003 B2 19930729
US 1994-254823 A2 19940613
OTHER SOURCE(S): MARPAT 128:321569
GI



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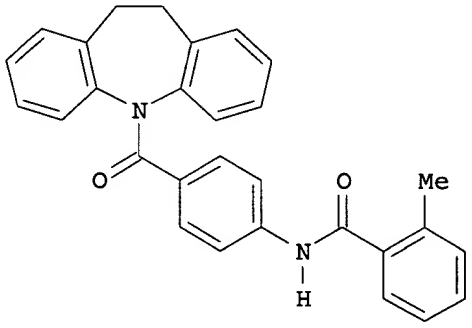

II

AB The title compds. [I; Y = a bond; AB = (CH2)2N(R3); R1 = H, halo, OH, etc.; R2 = H, halo, OH, etc.; R1R2 = methylenedioxy, ethylenedioxy; R3 = C(O)Ar (wherein Ar = (un)substituted Ph, thienyl, etc.); Z = (un)substituted fused benzo, thiazole, etc.], which exhibit antagonistic activity at V1 and/or V2 receptors, in vivo vasopressin antagonist activity, and antagonistic activity at oxytocin receptors, and therefore useful in treating diseases characterized by excess renal reabsorption of water such as congestive heart failure, nephrotic syndrome, hyponatremia, coronary vasospasm, cardiac **ischemia**, liver cirrhosis, brain edema, cerebral **ischemia**, or cerebral hemorrhage-stroke, were prepd. Thus, reaction of 4-[(2-methylbenzoyl)amino]benzoyl chloride with 10,11-dihydro-5H-dibenz[b,f]azepine in the presence of 4-(dimethylamino)pyridine in pyridine afforded the title compd. II which showed IC50 of 2.5 .mu.M against rat hepatic V1 receptors binding and IC50 of 0.86 .mu.M against rat kidney medullary V2 receptors binding.

L11 ANSWER 5 OF 6 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:567275 CAPLUS

DOCUMENT NUMBER: 125:221884
TITLE: Preparation of tricyclic benzazepines and benzodiazepines as vasopressin antagonists
INVENTOR(S): Albright, Jay Donald; Venkatesan, Aranapakam Mudumbai;
Delos Santos, Efren Guillermo
PATENT ASSIGNEE(S): American Cyanamid Company, USA
SOURCE: PCT Int. Appl., 357 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9622282	A1	19960725	WO 1996-US1051	19960116
W: AL, AM, AU, BB, BG, BR, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, LK, LR, LT, LU, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, UZ, VN, AZ, BY, KG, KZ, RU, TJ, TM				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5849735	A	19981215	US 1995-548805	19951222
AU 9649042	A1	19960807	AU 1996-49042	19960116
BR 9606977	A	19971104	BR 1996-6977	19960116
EP 804420	A1	19971105	EP 1996-905227	19960116
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV				
JP 10512865	T2	19981208	JP 1996-522448	19960116

PRIORITY APPLN. INFO.:
US 1995-373169 A 19950117
US 1995-548805 A 19951222
WO 1996-US1051 W 19960116

OTHER SOURCE(S): MARPAT 125:221884
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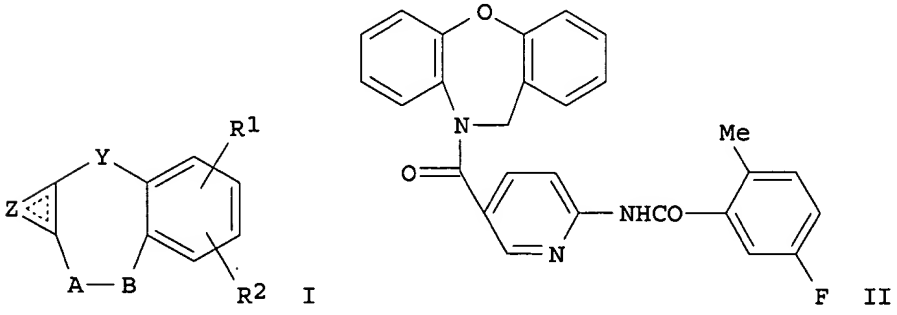

AB The title compds. [I; Y = (CH2)n (wherein n = 0-2), O, S, etc.; AB = (N-substituted) (CH2)mNH, NH(CH2)m (wherein m = 1-2); R1, R2 = H, halo, OH, etc.; Z = (substituted) fused Ph, 5-membered fused heteroaryl, etc.] which exhibit antagonist activity at V1 and/or V2 receptors and therefore useful as diuretics and antihypertensives, and in the treatment and/or prevention of congestive heart failure, liver cirrhosis, brain edema, cerebral **ischemia**, cerebral hemorrhage-stroke, thrombosis-bleeding, etc., were prepd. Thus, reaction of 10,11-dihydrodibenz[b,f][1,4]oxazepine with 6-[(5-fluoro-2-

methylbenzoyl)amino]pyridine-3-carbonyl chloride in the presence of Et3N in CH2Cl2 afforded the desired product II which showed IC50 of 0.24 .mu.M against rat hepatic V1 receptors and of 0.054 .mu.M against rat kidney medullary V2 receptors.

L11 ANSWER 6 OF 6 CAPLUS COPYRIGHT 2001 ACS
ACCESSION NUMBER: 1996:422349 CAPLUS
DOCUMENT NUMBER: 125:86656
TITLE: Novel adamantyl-containing heterocyclic alkylamino derivatives as sigma 2 selective ligands.
INVENTOR(S): Rocher, Jean-Philippe
PATENT ASSIGNEE(S): Mitsubishi Chemical Corporation, Japan
SOURCE: PCT Int. Appl., 185 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9605185	A1	19960222	WO 1995-JP1600	19950810
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RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
CA 2197172	AA	19960222	CA 1995-2197172	19950810
EP 777660	A1	19970611	EP 1995-928013	19950810
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
CN 1164856	A	19971112	CN 1995-195552	19950810
JP 10508826	T2	19980902	JP 1995-507194	19950810

PRIORITY APPLN. INFO.: GB 1994-16571 19940816
WO 1995-JP1600 19950810
OTHER SOURCE(S): MARPAT 125:86656
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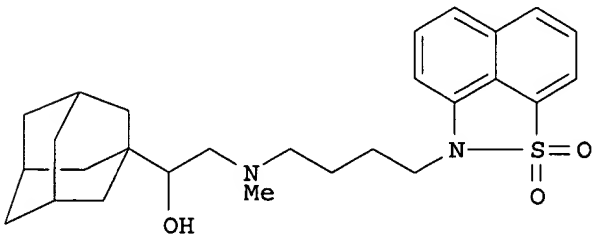

II

AB The invention relates to novel alkylamino derivs. AC(X)(Y)CR1R2NR3R4 [I; A = OH, (cyclo)alkoxy, alkenyloxy, aryloxy, aralkoxy, (a)cyclic amino, etc.; X = cycloalkylalkyl or adamantyl and Y = H, (un)substituted alk(en/yn)yl, adamantyl, (hetero)aryl, etc.; or X = cycloalkyl and Y = H, alk(en)yl, cycloalkyl; or AY = O or NOH; R1, R2 = H, alk(en)yl, cycloalkyl, hydroxyalkyl; R3 = alk(en)yl, cycloalkyl, hydroxyalkyl; R4 = (CH2)pB; p = 3-8; or NR3R4 = certain substituted piperidino groups; B = certain N-bound, N-contg., polycyclic heterocycles] and their pharmaceutically

acceptable salts, hydrates, and solvates. I exhibit high selectivity and affinity for .sigma.2-receptors, and therefore are useful in the treatment of central nervous system disorders, as well as other disorders (e.g., cardiovascular) modulated by this receptor. For example, 2-(4-chlorobutyl)-2H-naphth[1,8-c,d]isothiazole 1,1-dioxide underwent a sequence of halogen exchange with iodide (81%), aminolysis of the iodobutyl compd. with CF3CONHMe and NaH in DMF (40%), methanolysis of the obtained trifluoroacetamide deriv. (76%), N-alkylation with 1-(bromoacetyl)adamantane using K2CO3 in MeCN (57%), and redn. of the keto function with NaBH4 (85%), to give title compd. II (isolated as the fumarate, 73%). II had an oral ED50 of 0.3 mg/kg for protection of mice from mescaline-induced scratching. II also showed a .sigma.2/.sigma.1 Ki ratio of 0.01, vs. a ratio of 24 for haloperidol. I generally had an oral LD50 > 1000 mg/kg in mice, with no cataleptic effects.

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L3           321 S ?PHENANTHRIDINONE
L4           349 S ?PHENANTHRIDINONE?
L5          2409 S PARP
L6            28 S L5 AND L4
L7            18 DUPLICATE REMOVE L6 (10 DUPLICATES REMOVED)
L8        139651 S ISCHEMIA
L9            15 S L8 AND L4
L10            6 S L9 NOT L6
L11            6 DUPLICATE REMOVE L10 (0 DUPLICATES REMOVED)

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FULL ESTIMATED COST                                61.57      61.87

DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS)      SINCE FILE      TOTAL
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